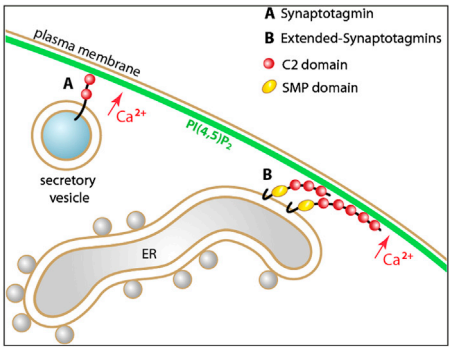
In This Issue

Cell



Ca^{2+} Matchmaker for EM and Plasma Membrane

PAGE 1494

Endoplasmic reticulum (ER)-plasma membrane (PM) contacts are ubiquitous but mysterious structures thought to be important for regulation of intracellular Ca^{2+} dynamics. Giordano et al. report that the extended synaptotagmins (E-Syts) are ER proteins that tether the ER to the PM but are not required for regulation of ER Ca^{2+} stores. ER-PM tethering via E-Syt complexes is induced by elevated cytosolic Ca^{2+} levels, suggesting that cellular signaling pathways can specifically trigger the formation of ER-PM contact sites.

Gut Reaction to Aging Starts in the Mind

PAGE 1435

The unfolded protein response (UPR) helps cells process misfolded proteins, but the ability of cells to mount UPR declines with age. Taylor et al. show that in *C. elegans* constitutive expression of the UPR transcriptional regulator XBP-1 can rescue the age-related loss in UPR and extend lifespan. Surprisingly, XBP-1 elicits these effects non-cell-autonomously through its expression in neurons, which activate UPR in intestinal cells, likely via neurotransmitter release.

Sirtuin Watches Over Aging Clocks

PAGE 1448

SIRT1, a NAD-dependent deacetylase, regulates various metabolic processes, including aging. Chang and Guarente show that SIRT1 also regulates the central circadian oscillator in the mouse brain by activating transcription of BMAL1, a clock component. The clock's ability to adapt to changes in light-dark cycles (similar to overcoming jet lag) declines with age, as do SIRT1 levels. Importantly, overexpression of SIRT1 in the brain partially protects mice from this decline in circadian adaptability, linking SIRT1 to aging-related changes in circadian rhythms.

Out, Damned Stress Granules!

PAGE 1461

RNA and protein-containing aggregates, comparable to stress granules and P bodies, are hallmarks of several neurogenerative diseases. Buchan et al. develop a yeast screen for proteins influencing stress granule levels and demonstrate that levels of these assemblies are modulated by autophagic clearance, involving Cdc48 and its mammalian homolog VCP. The findings suggest avenues for targeting pathological RNA-containing aggregates and for identifying factors contributing to their genesis.

One Degree of Separation for Avian Flu

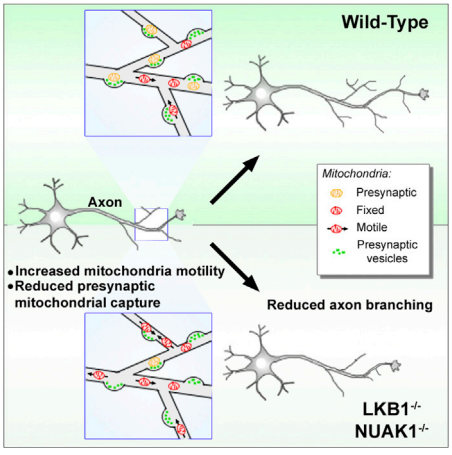
PAGE 1475

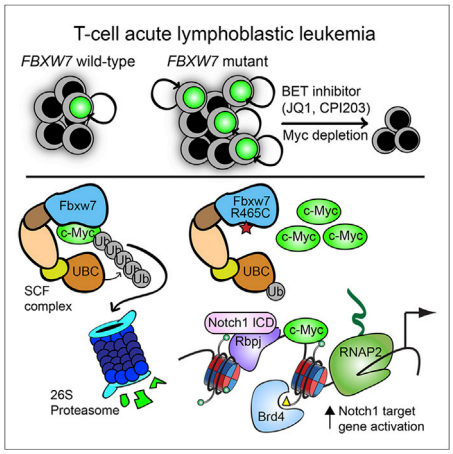
Analyses by Tharakaraman et al. of the structural features of hemagglutinin from avian influenzas H5N1 and H7N9, the latter identified only earlier this year, suggest that circulating strains may require just one amino acid change to switch their binding preferences from avian to human receptors. These studies enable the surveillance of avian influenza strains that may be closest to human adaptation and, given their pandemic potential, have ramifications for vaccine development.

Axons Branch Where Mitochondria Brake

PAGE 1510

Mammalian cortical neurons undergo extensive branching to be able to establish thousands of synapses. Courchet et al. report that the LKB1-NUAK1 kinase pathway regulates axon branching by impacting mitochondrial trafficking patterns in axons and increasing the number of mitochondria captured at nascent synapses. The findings reveal a link between mitochondrial dynamics and neuronal morphogenesis.





Selective Stability in Leukemia

PAGE 1552

King et al. study missense mutations in the ubiquitin ligase FBXW7 that are associated with the initiation and progression of T cell acute lymphoblastic leukemia. They find that these mutations, together with mutations in Notch1, specifically augment the function of leukemia-initiating cells without disrupting the function of normal hematopoietic stem cells and that FBXW7 regulates c-Myc stability. Significantly, reducing c-Myc activity leads to leukemia remission, suggesting a therapeutic approach for treating this aggressive disease.

Cortical Anchor Cures Dynein Wanderlust

PAGE 1526

Dynein is well characterized as a minus-end-directed microtubule motor. By visualizing single dyneins in vivo during meiosis in fission yeast, Ananthanarayanan et al. find that they exhibit bidirectional diffusive motion upon initial microtubule binding and that the motor's motion becomes directional only upon binding to proteins anchoring them to the cell cortex. This behavior allows dyneins to accumulate at sites where they can exert large forces such as those required for nuclear oscillations.

Allowing Xist to Exist

PAGE 1537

The Xist noncoding RNA promotes inactivation of one X chromosome in female mammals by coating that chromosome and recruiting silencing complexes. Xist expression is controlled by X-linked activators and autosomal repressors. Sun et al. now show that the X-linked Jpx noncoding RNA is a dose-sensitive activator of Xist that acts by titrating the autosomal transcription factor CTCF (a repressor of *Xist*) away from the *Xist* promoter, delineating a new mechanism of epigenetic regulation by a noncoding RNA.

A Condo of Organisms, Village of Genes

PAGE 1567

A species of mealybugs, common plant pests, harbors two bacterial symbionts in a matryoshka-doll-like arrangement, one species of bacteria nesting within the other's cytoplasm. Husnik et al. find that the larger of these bacteria has undergone massive genome reduction, akin to that of the mitochondrial genome, but surprisingly not due to the transfer of genes to its cosymbionts. Instead, horizontal transfer of vital genes from multiple diverse microbes to the insect's genome allows the triple symbiont to survive.

Evolution Is a Smooth Operator

PAGE 1579

The prediction and experimental verification of adaptive trajectories on macroevolutionary timescales have rarely been achieved for complex biological systems. Modeling photosynthesis evolution, Heckmann et al. simulate likely sequences of evolutionary changes from C_3 to C_4 photosynthesis biochemistry. Measured parameters from C_3-C_4 intermediate plants lie close to the mean predicted evolutionary path. Adaptation is predicted to proceed at an almost constant rate, giving the biochemical fitness landscape an exceedingly simple, smooth Mount-Fuji-like structure.

Modeling Translation from Start to Finish

PAGE 1589

Shah et al. develop a computational model of translation, tracking every ribosome, tRNA, and mRNA molecule in a yeast cell. They use the model to infer initiation rates for translating yeast mRNAs and attribute increased ribosome density at the 5′ends of transcripts to rapid initiation on short genes. They additionally identify factors that contribute to protein yield under different conditions. Taken together, these insights suggest that protein production is limited by the availability of free ribosomes.

Rev-eel-ing an Inducible Fluorescent Protein

PAGE 1602

Kumagai et al. identify the first vertebrate fluorescent protein, derived from Japanese eels. UnaG, a protein belonging to the fatty-acid-binding protein (FABP) family, produces oxygen-independent green fluorescence upon binding to bilirubin. Using structural and biochemical approaches, the authors develop a simple and rapid fluorescent-based human bilirubin assay with promising clinical utility.